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Reconstructing cell cycle and disease progression using deep learning

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Catalog

Abstract

Deep convolutional neural networks combined with nonlinear dimension reduction enable reconstructing biological processes
based on raw image data.
In this article , the author demonstrates this by reconstructing the cell cycle of Jurkat cells and disease progression in diabetic retinopathy.

In further analysis of Jurkat cells, we detect and separate a subpopulation of dead cells in an unsupervised manner and, in classifying discrete cell cycle stages, we reach a sixfold reduction in error rate compared to a recent approach based on boosting on image features.

In contrast to previous methods, deep learning based predictions
are fast enough for on-the-fly analysis in an imaging flow cytometer.

Introduction

Keywords:

Deep learning (Method of data representation learning , from ANN)

CNN (one of FNN , including (convolutional layer) and (pooling layer))

Boosting (It is a method to improve the **accuracy** of any given learning algorithm)

T-SNE (Unsupervised learning, A method of dimensionality reduction for data)

Jurkat cells (A suspension cell line of acute T cell leukemia)

Flow cytometer

Diabetic retinopathy

Introduction

Background:

A major challenge and opportunity in biology is interpreting the increasing amount of information-rich and high-throughput single-cell data.

Here, we focus on imaging data from **fluorescence microscopy**, in particular from imaging flow cytometry (IFC), which combines the **fluorescence sensitivity** and **high-throughput capabilities** of flow cytometry with single-cell imaging.

Deep learning is therefore capable of processing the dramatic increase in information content—compared to spatially integrated fluorescence intensity measurements as in conventional flow cytometry—in IFC data

Introduction

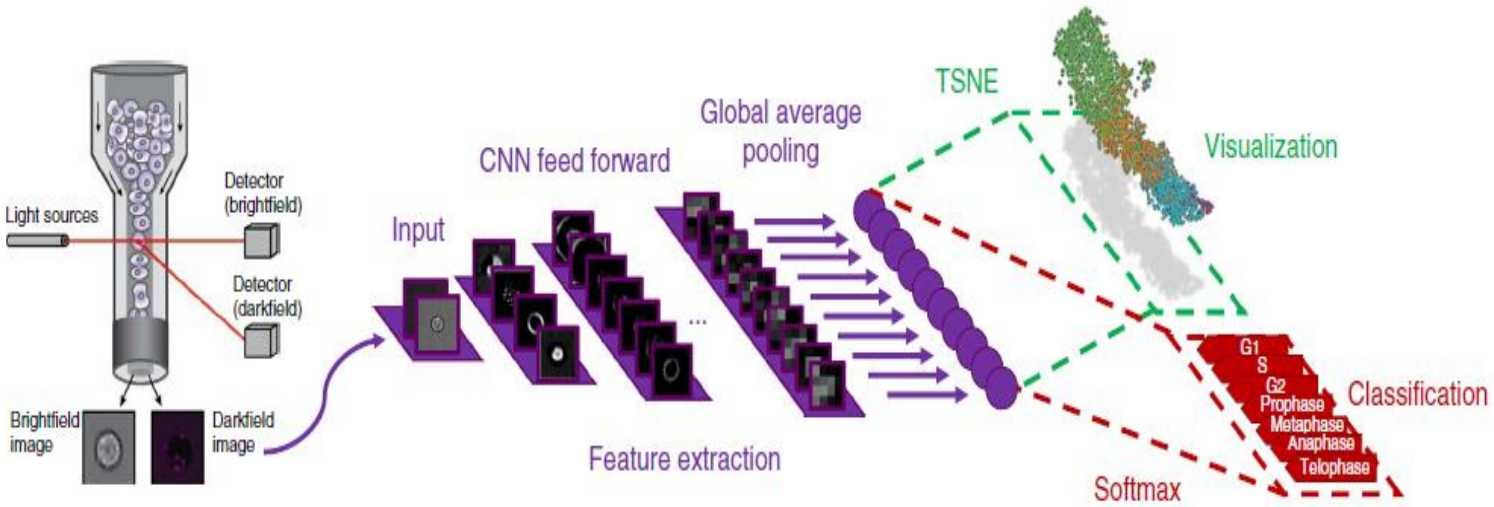
Background:

While this is possible for cell cycle when carrying out elaborate experiments where such markers are measured, in many other cases, this is too tedious, has severe side effects with unwanted influences on the phenomenon itself or is simply not possible as markers for a specific phenomenon are not known

Therefore, we propose a general workflow that uses a deep convolutional neural network combined with classification and visualization based on nonlinear dimension reduction

Introduction

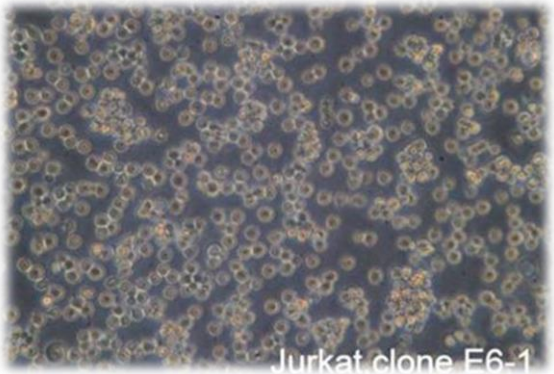
Background:



Data and Method

Data

From 32,266 Jurkat cells



Method

PI （碘化丙啶）

MPM2 （有丝分裂蛋白单克隆**#2**）

DeepFlow

Result and Analysis

1.Reconstructing cell cycle progression

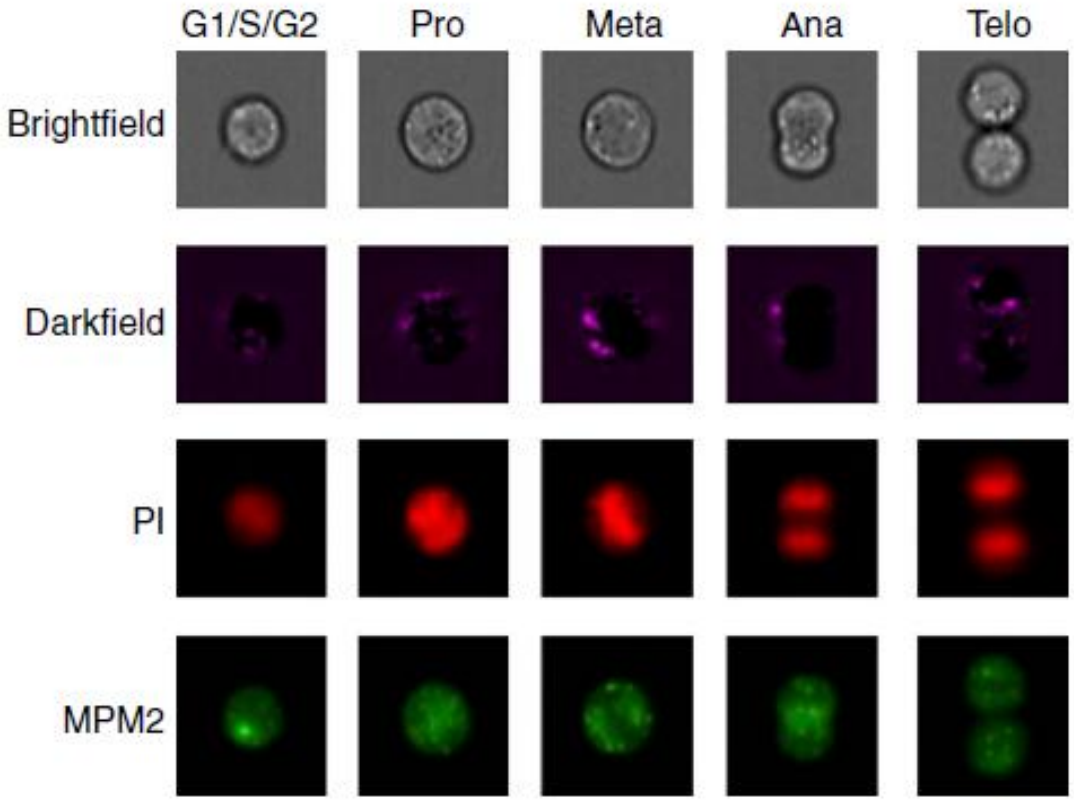
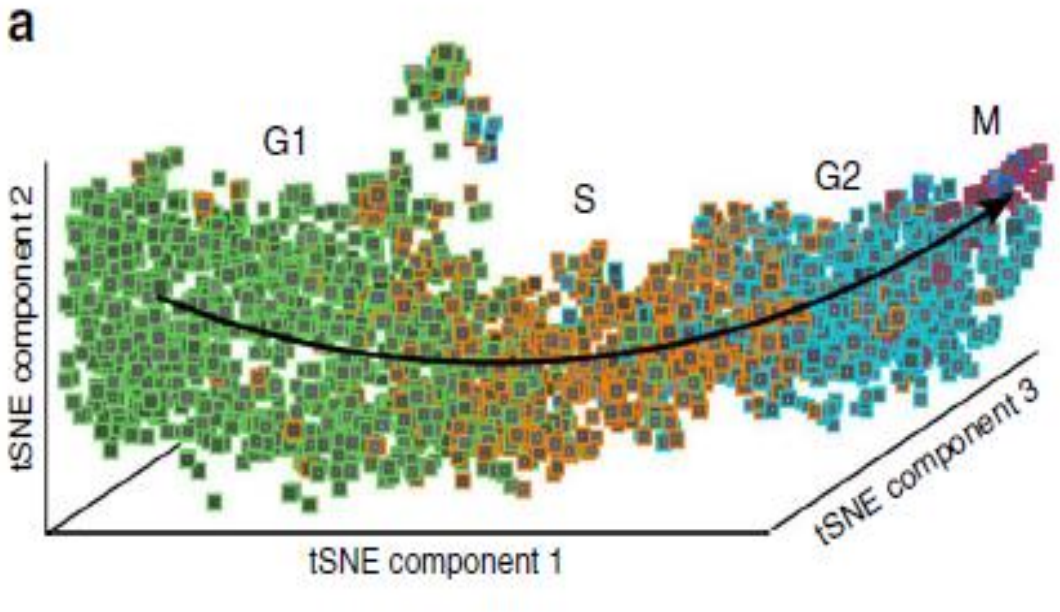


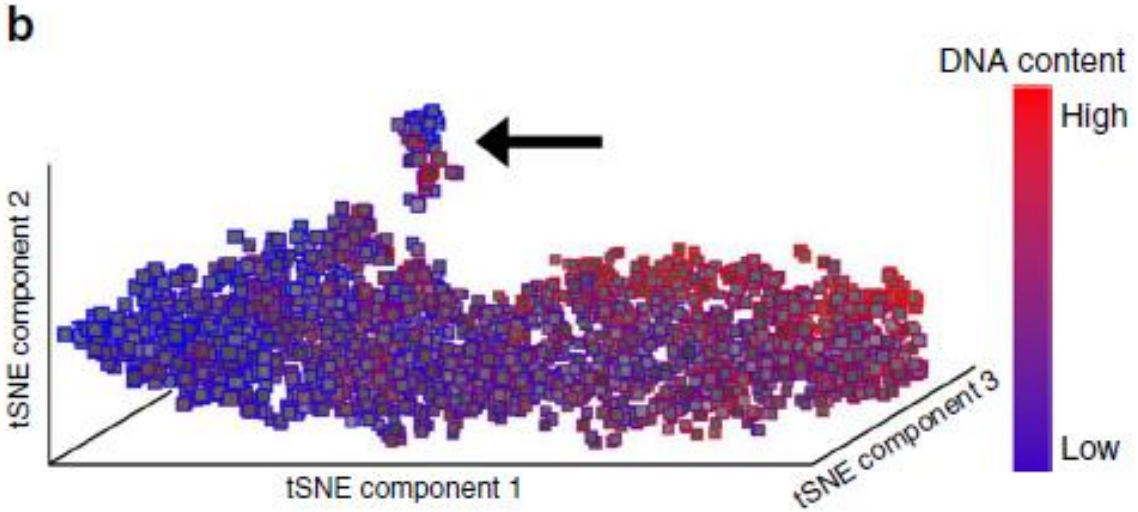
Fig. 2 Representative images for the cell cycle stages as measured in brightfield, darkfield, and fluorescence channels. Seven cell cycle stages define seven classes. We only show one representative image for the interphase classes G1, S, and G2, which can hardly be distinguished by eye

Result and Analysis



We observe that the Jurkat cell data is organized in a long stretched cylinder along which cell cycle phases are ordered in the chronologically correct order

Result and Analysis

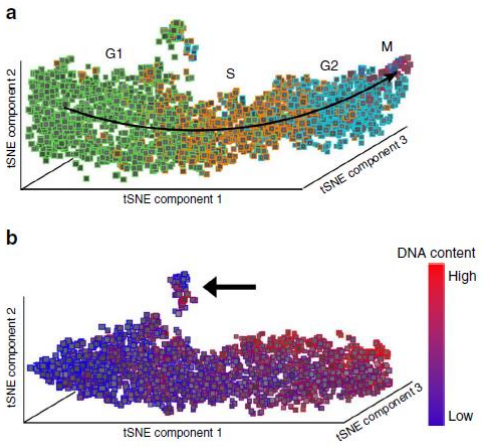


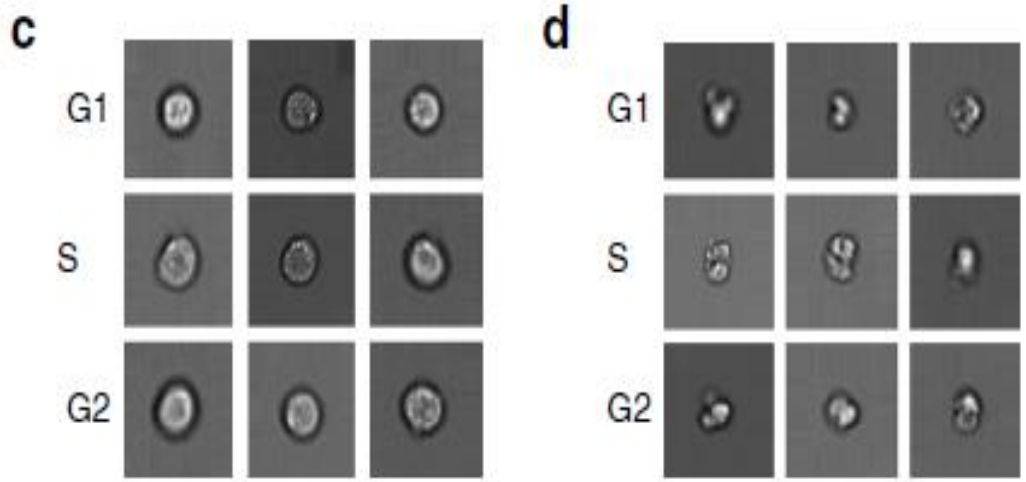
We separately visualized just those cells annotated as being in the interphase classes (G1, S, G2) and colored them with the DNA content obtained from one of the fluorescent channels of the IFC.

The DNA content reflects the continuous progression of cells in G1, S, and G2 on a more fine-grained level. Its correspondence with the longitudinal direction of the cylinder found by tSNE demonstrates that the temporal order learned by the neural network is accurate even beyond the categorical class labels.

Result and Analysis

2.Detecting abnormal cells in an unsupervised manner

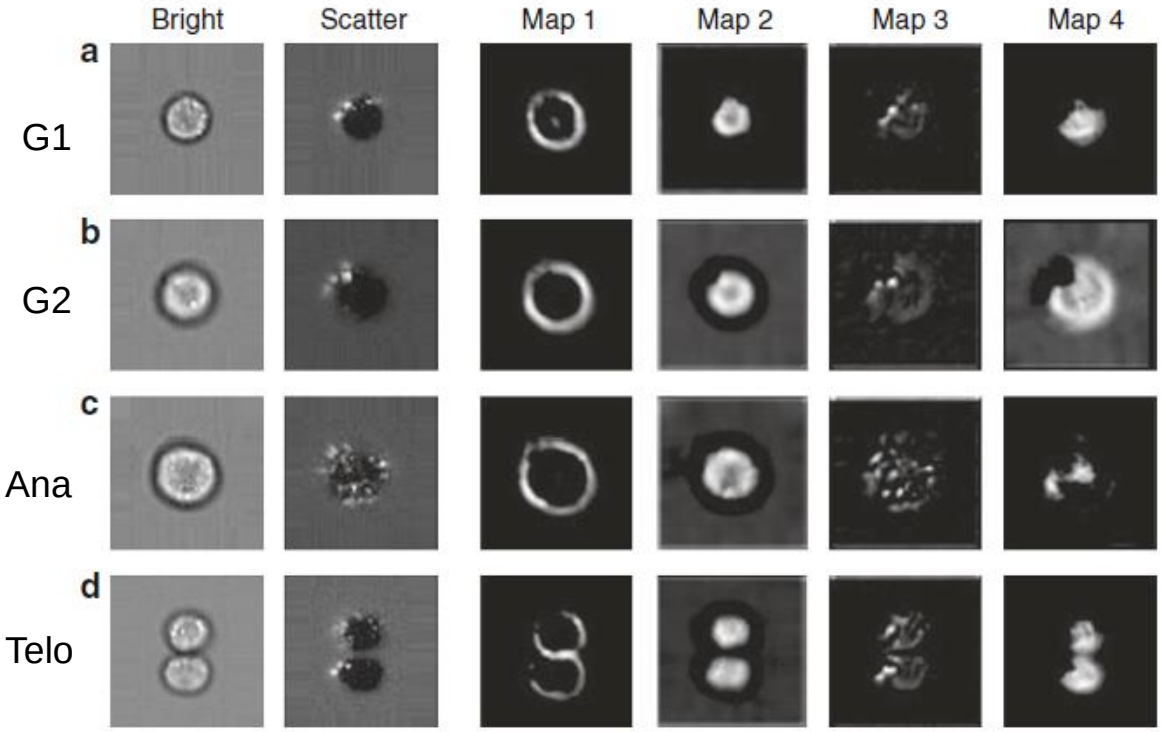




It contains cells from all three interphase classes. While cells in the bulk have high circularity and well defined borders (Fig. 3c)
cells in the small cluster are characterized by morphological abnormalities such
as broken cell walls and outgrowths, signifying dead cells (Fig. 3d).

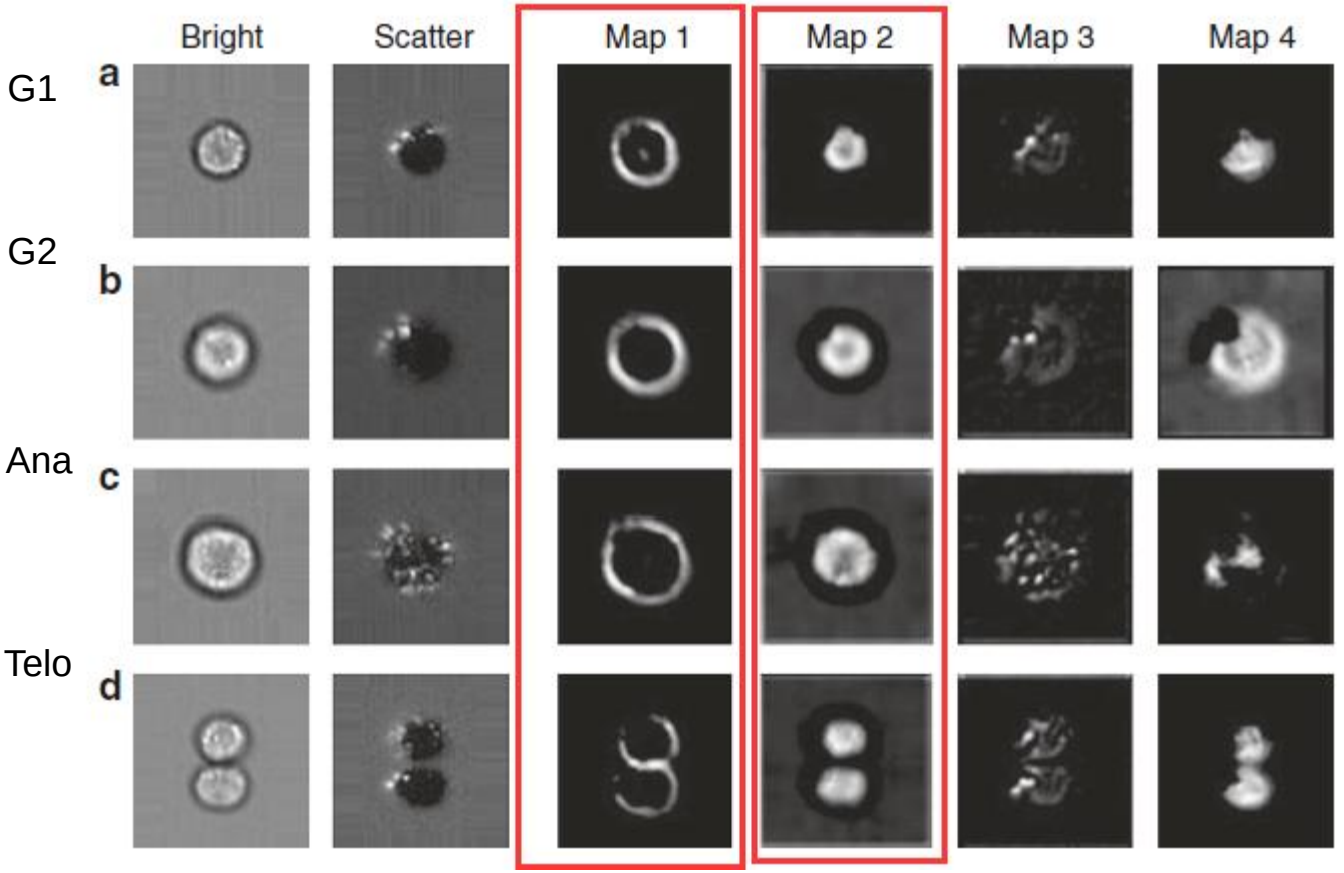
Result and Analysis

3.Deep learning automatically performs segmentation



We interpret the data representation encoded in one of the trained intermediate layers of the neural network by inspecting its activation patterns using exemplary input data from several classes

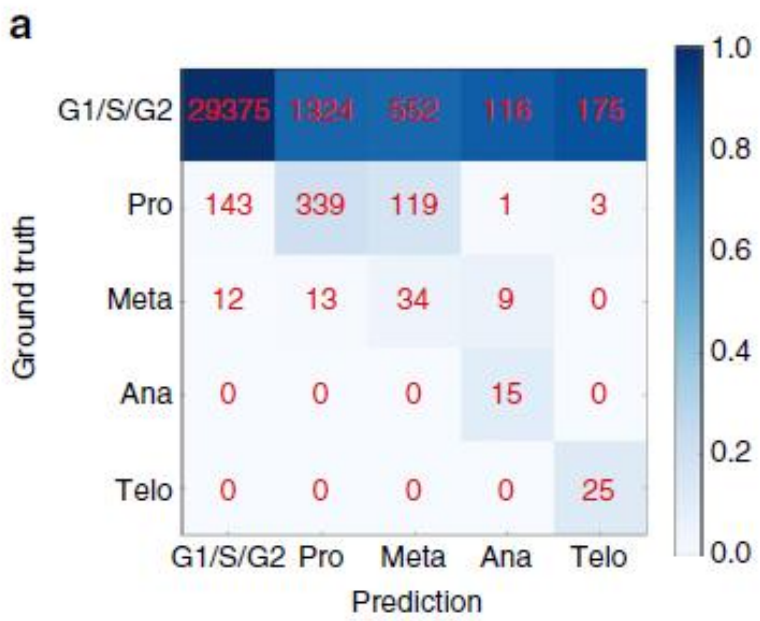
Result and Analysis

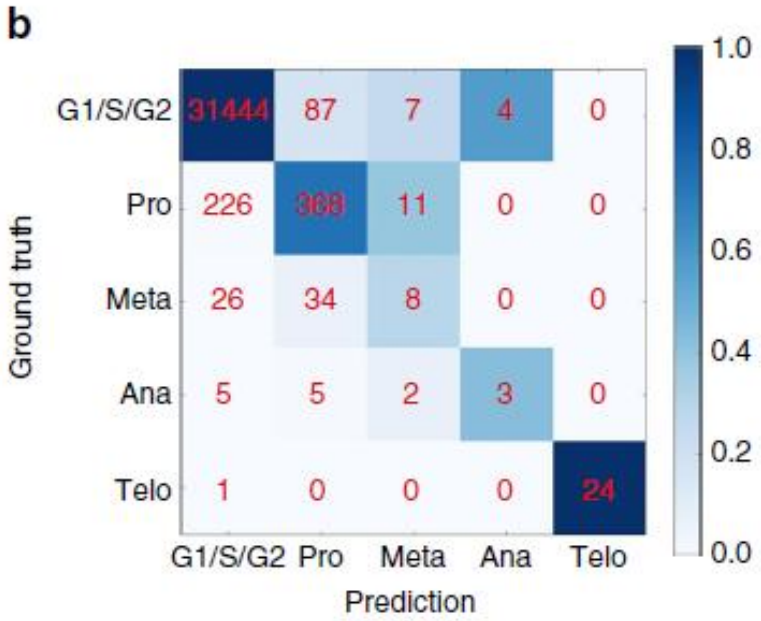


We observe a strong response to features that arise from **the cell border thickness** (Fig. 4, map 1), to **area-based features** (Fig. 4, map 2), as well as **cross-channel features.**

Result and Analysis

4.Deep learning outperforms boosting for cell classification



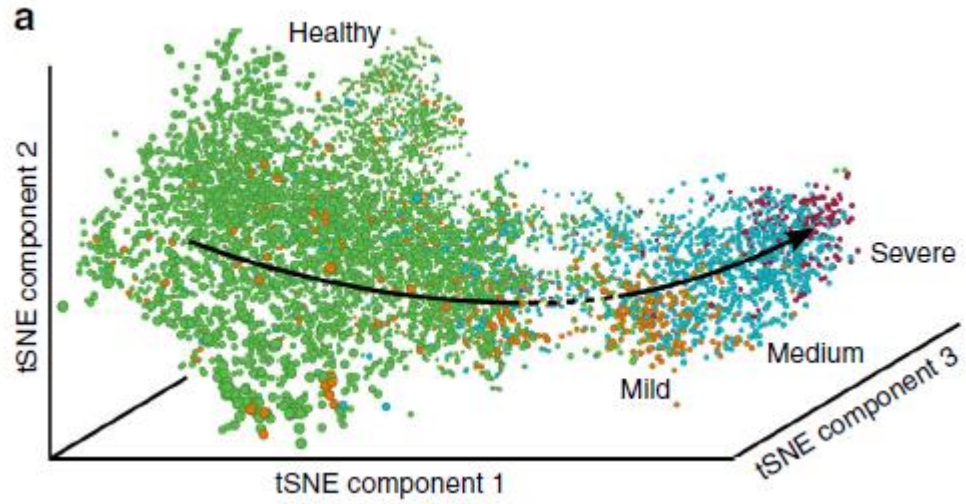


Boosting ： 92.53%

Deep Learning：98.73%±0.16%

Result and Analysis

5.Reconstructing disease progression



30,000 color fundus photographies of the human retina

We observe a reconstructed disease progression (Fig. 6) for 8000 samples in the validation data set, that is, the four disease states are ordered along disease severity, even though the network has not been provided with the ordering information.

Discussion

Given the compelling performance on reconstructing the cell cycle and diabetic retinophany, we expect deep learning to be helpful for understanding **a wide variety of biological processes** involving continuous morphology changes.

Examples include developmental stages of organisms, dose response and the progression of healthy states to disease states, situations that have often been
non-ideally reduced to binary classification problems

Our results indicate that reconstructing biological processes is possible
for a wide variety of image data, if enough samples are available.

Bright spot

Only one of the other recent works on deep learning in high-throughput microscopy discusses the **visualization of network features**, but none deal with continuous biological processes

Inspiration

In scientific research, we must learn to learn from the crowd, the theory and technology to be integrated

Deficiencies

The direction of disease progression is not universal, only one

The process of cell cycle is not more refined

Thanks for your attention